The AGNP-TDM Expert Group Consensus Guidelines: focus on therapeutic monitoring of antidepressants

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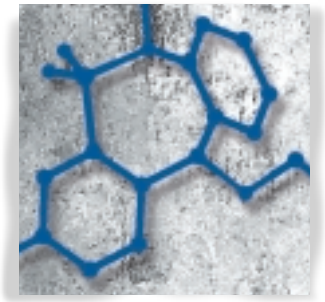

Pharmacopsychiatry and psychotherapy are beneficial for many patients with depression. Evidence-based and clinical experience collected during the past decades has allowed the introduction of guidelines and recommendations from experts in the field[1-3] to optimize antidepressant pharmacotherapy. However, partial response and nonresponse are frequent,[4] despite the introduction of new psychotropic agents, including "third-generation antidepressants,"[5] and amelioration and remission rates are still far from optimal. The efficacy of available drugs can be increased, not only by the

Therapeutic drug monitoring (TDM) of psychotropic drugs such as antidepressants has been widely introduced for optimization of pharmacotherapy in psychiatric patients. The interdisciplinary TDM group of the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie *(AGNP) has worked out consensus guidelines with the aim of providing psychiatrists and TDM laboratories with a tool to optimize the use of TDM. Five research-based levels of recommendation were defined with regard to routine monitoring of drug plasma concentrations: (i) strongly recommended; (ii) recommended; (iii) useful; (iv) probably useful; and (v) not recommended. In addition, a list of indications that justify the use of TDM is presented, eg, control of compliance, lack of clinical response or adverse effects at recommended doses, drug interactions, pharmacovigilance programs, presence of a genetic particularity concerning drug metabolism, and children, adolescents, and elderly patients. For some drugs, studies on therapeutic ranges are lacking, but target ranges for clinically relevant plasma concentrations are presented for most drugs, based on pharmacokinetic studies reported in the literature. For many antidepressants, a thorough analysis of the literature on studies dealing with the plasma concentration–clinical effectiveness relationship allowed inclusion of therapeutic ranges of plasma concentrations. In addition, recommendations are made with regard to the combination of pharmacogenetic (phenotyping or genotyping) tests with TDM. Finally, practical instructions are given for the laboratory practitioners and the treating physicians how to use TDM: preparation of TDM, drug analysis, reporting and interpretation of results, and adequate use of information for patient treatment. TDM is a complex process that needs optimal interdisciplinary coordination of a procedure implicating patients, treating physicians, clinical pharmacologists, and clinical laboratory specialists. These consensus guidelines should be helpful for optimizing TDM of antidepressants.*

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Selected abbreviations and acronyms

CYP	*cytochrome P-450*
GC	*gas chromatography*
HPLC	*high-performance liquid chromatography*
LOD	*limit of detection*
LOQ	*limit of quantification*
PM	*poor metabolizer*
SSRI	*selective serotonin reuptake inhibitor*
TDM	*therapeutic drug monitoring*
UM	*ultrarapid metabolizer*

use of augmentation strategies[6,7] and other combination treatments,[8,9] but also by analysis of antidepressant drug concentrations in blood plasma.[10] Recently, a group of psychiatrists, clinical pharmacologists, biochemists, and clinical chemists, all members of the AGNP (Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie; www.agnp.de), worked out consensus guidelines for therapeutic drug monitoring (TDM) in psychiatry, after they had compiled information from the literature.[11] These guidelines were mainly based on the hypothesis that some inadequate or insufficient treatments of psychiatric patients can be explained by the fact that psychotropic drugs not only differ in their pharmacological profile, but also in their metabolism and pharmacokinetics in the individual patient. Treatment should therefore be adapted according to this situation by using TDM and pharmacogenetic tests. This combined strategy takes into consideration the fact that the fate of the drug depends on both environmental (diet, smoking habits, comorbidities, and comedications) and genetic factors.

Pioneering work in this field was mainly carried out in Sweden, where the first study on the plasma concentration–clinical effectiveness relationship of an antidepressant (nortriptyline)[12] was performed. This was an outstanding demonstration of the usefulness of the combination of TDM and pharmacogenetic tests (CYP 2D6) in a pharmacovigilance case situation.[13] Over the past 20 years, TDM for antidepressants has been widely introduced, but consensus guidelines published to date, or other state-of-the-art reports on the use of TDM for antidepressants concentrated primarily on tricyclic drugs.[14-17] There is an increasing trend to recommend TDM in combination with pharmacogenetic tests.[18,19]

Aims of the consensus document

The present consensus guidelines were elaborated to assist psychiatrists, laboratory practitioners, and heads of laboratories involved in psychopharmacotherapy to optimise the use of TDM. Here we focus on antidepressants,* and give recommendations on how to use TDM and genotyping/phenotyping procedures.

Pharmacokinetics, metabolism, and pharmacogenetics of antidepressants

Antidepressants share many common features, such as high lipophilicity, a molecular weight between 200 and 500, and basicity. We therefore present a general summary of their pharmacokinetic properties in *Table I*,[20-26] though numerous compounds constitute exceptions: citalopram is known for its high bioavailability (about 90%) and relatively low binding to plasma proteins (80%); venlafaxine, trazodone, tranylcypromine, and moclobemide display a short (about 2-10 h) and fluoxetine a long plasma half-life (3-15 days, taking into account its active metabolite). It should also be considered that many antidepressants, such as venlafaxine, citalopram,

*This review takes into consideration antidepressant agents currently available in Switzerland and Germany, and therefore does not claim to be exhaustive.

Keywords: *therapeutic drug monitoring; antidepressant; consensus guidelines; pharmacotherapy; psychiatry*

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and mirtazapine, are used as racemic compounds, the enantiomers of which differ in their pharmacological, metabolic, and pharmacokinetic properties.[27,28]

Most antidepressants undergo phase I metabolism by oxidation, such as aromatic ring and aliphatic hydroxylation, N- and O-dealkylation, N- and O-oxidation to N-oxides, carbonyl reduction to secondary alcohols, and S-oxidation to sulfoxides or sulfones, which results in an increase in polarity.[29] The introduction of a functional group (eg, a hydroxy group) or the presence of a tertiary amine group may enable a phase II metabolic step, typically a glucuronidation.[30-32] Metabolism occurs mainly in the liver and in the intestinal mucosa. It may be age-dependent, and vary as a consequence of the influence of environmental factors, such as somatic diseases, comedication, food, and smoking. TDM should include the assay of active metabolites[33-35] (eg, clomipramine [norclomipramine] and fluoxetine [norfluoxetine]), but the parent compound/inactive metabolite ratio may be helpful to evaluate the metabolic state or compliance of the patient.

Considerable and clinically relevant knowledge has been acquired during the past 30 years on the important role of cytochrome P-450 (CYP) isozymes, CYP 1A2, CYP 2D6, CYP 2C9, CYP 2C19, and CYP 3A4/5, in the biotransformation of antidepressants.[36-42] The genetically determined polymorphism of CYP 2D6 is of high clinical relevance for antidepressants, which are substrates of this isozyme, including tricyclic antidepressants, some selective serotonin reuptake inhibitors (SSRIs) (eg, paroxetine and fluoxetine), and "third-generation" antidepressants (eg, venlafaxine and mirtazapine). About 5% to 8% and 1% to 7% of the Caucasian population are considered as poor metabolizers (PMs) or ultrarapid metabolizers (UMs), respectively *(Table I)*.[22,43,44] In Caucasians, there is a lower proportion (3%-5%) of PMs of CYP 2C19, which is frequently involved in N-demethylation of tertiary amines (amitriptyline and citalopram). CYP 3A4/5 shows wide interindividual variability in its activity. CYP 3A5 is expressed in only one-third of the Caucasian population.[45] As regards CYP 1A2, only its inducibility (eg, by tobacco smoke) is genetically polymorphic.[46,47] Clinically, a PM status may represent a higher risk for adverse effects in patients treated with antidepressants known to be substrates of the deficient enzyme, while UMs undergo a higher risk for nonresponse, due to subtherapeutic plasma concentrations.[39,48-53] The clinical relevance of the genetic

Pharmacokinetic phase		Characteristics
Absorption	**A**	Good absorption from gastrointestinal tract
		Maximum plasma concentration within a short time after administration (t_{max} of about 0.5 to 4 h)
Distribution	**D**	High distribution volume
		Fast distribution from plasma to the central nervous system
		10 to 40 times higher levels in brain than in blood
		Possible regulation of transport intestine–blood and blood–brain by transport proteins (P-glycoprotein)
		Low plasma concentrations in steady-state conditions (trough levels: 0.5-500 ng/mL)
		High plasma protein binding (90%-99%)
Metabolism	**M**	Metabolism: a prerequisite for excretion
		High first-pass metabolism (systemic availability: 10%-70%)
		Main metabolic enzyme systems: cytochrome P-450, UDP-glucuronosyltransferases
		Genetic polymorphisms for some enzymes (extensive, intermediate, poor, and ultrarapid metabolizers)
		Inducibility of some enzymes by drugs or other xenobiotics
		Generally formation of active, but more polar metabolites
		Occurrence and relevance of metabolism in brain doubtful
		Important effect of hepatic insufficiency on hepatic elimination
		High risk for inhibition of drug metabolism by comedication, inhibitors of cytochrome P-450
Elimination	**E**	Low renal excretion
		Small effect of renal insufficiency on plasma kinetics of drug and its metabolites
		Slow elimination from plasma (half-life 12-36 h), mainly by hepatic metabolism
	ADME	Linear pharmacokinetics at clinically relevant doses

Table I. General pharmacokinetic properties (absorption, distribution, metabolism, and elimination [ADME]) of antidepressants.[11,20]

polymorphisms of UDP-glucuronosyltransferases in pharmacopsychiatry is not clear.[30,54]

Genotyping, which represents a "trait marker," is readily available and clinically recommended for CYP 1A2, CYP 2C9, CYP 2C19, CYP 2D6, and CYP 3A4/5; phenotyping, used as a "state-marker," may be performed for the same enzymes. The result of genotyping is not influenced by environmental factors and has life-long validity. Phenotyping requires the administration of drugs and is therefore a more invasive procedure. Therefore, indications for phenotyping and genotyping may differ.

As mentioned in *Table I*, transport proteins such as P-glycoprotein in the intestinal mucosa and in the blood–brain barrier may be implicated in the regulation of the availability of antidepressants for the brain, but there is still a lack of clinical data.[55-57]

Relationships between drug doses, plasma concentrations, and clinical variables

TDM is based on the hypothesis assumption that there is a well-defined relationship between the drug plasma concentration and its clinical effects (therapeutic effect, adverse effects, and toxicity). However, while such a relationship is generally well admitted for lithium and for the tricyclic antidepressants nortriptyline, amitriptyline, desipramine, and imipramine, inconsistent results were obtained in studies on other tricyclic or similarly structured antidepressants, SSRIs, and other recently introduced antidepressants.[20,58-62] Interestingly, systematic reviews and meta-analyses[14,59] that were based on adequately designed studies yielded evidence of a relationship between clinical variables and plasma concentration for some tricyclic drugs. This suggests that numerous studies were poorly designed methodologically in order to demonstrate an evident relationship between concentration and effects or side effects. Recently, Ulrich and Läuter[60] defined criteria for quality assessment of TDM studies, which include the use of valid chemical and analytical methods, adequate psychopathology rating scales, appropriate selection criteria for patients (eg, exclusion of known nonresponders), and reporting of comedication.

Analytical procedures

Plasma or serum samples are generally used for TDM. Concentrations of antidepressants are low, most often in the nmol/L (ng/mL) range. Therefore, highly sensitive and selective analytical methods are needed for accurate and precise quantification.[63-66]

Most laboratories use now gas chromatography (GC) or high-performance liquid chromatography (HPLC) for the assay of antidepressants for TDM purposes. For GC, the most recommended detection systems are mass spectrometry (GC-MS) or nitrogen phosphor detectors (GC-NPD). Ultraviolet (UV) detectors, fluorescence detectors, and mass spectrometry (LC-MS), in increasing order, are useful for a selective and sensitive drug assay. Clearly, the need for sample preparation before chromatographic separation represents a time-consuming step, and this procedure also implies a limited sample throughput, despite the availability of automated sample preparation prior to GC or HPLC.[67] Direct injection ("column switching HPLC") of plasma or serum into the HPLC system is now available for a number of antidepressants.[68-70] LC-MS and LC-MS-MS (tandem mass spectrometry) will increasingly be the method of choice, as it may be applied to almost any psychotropic drug including metabolites, while GC-MS is applicable only for volatile compounds.

Economic aspects of TDM in psychiatry

TDM for a single psychoactive drug, including a metabolite, costs between 20 and 80 €, which includes costs for staff, instrumentation, chemicals, and other materials. In some countries, analyses may be billed according to the analytical technique used (higher rates for mass spectrometric quantification).

A proof of cost-effectiveness has been provided for only a few antidepressants.[71,72] However, additional studies are required. They should be designed to take account of the complexity of the TDM process *(Figure 1)*. For example, a recent prospective study carried out under naturalistic conditions showed that dose adjustment by the treating physician was frequently inappropriate, in that he or she neglected the results of the laboratory assays.[73]

Preliminary data suggest that phenotyping or genotyping of patients may help decrease the cost of their treatment with substrates of CYP 2D6.[74] The costs of treating patients who are either UMs or PMs (CYP 2D6) are seemingly thousands of US dollars per year higher than those for extensive metabolizers (EMs).[75] However, the tools to assess the cost-effectiveness of pharmacogenetic tests are still insufficiently developed.[76]

Consensus

TDM should be limited to situations where it may be expected that the result will help to solve a therapeutic problem. There are many indications for using TDM *(Table II)* in antidepressant pharmacotherapy, such as suspicion of noncompliance or intoxication. In pharmacovigilance programs, TDM may be considered as a valid indication for all drugs and groups of patients. To recommend TDM as routine monitoring, it must be proven that TDM is of value. Five levels of recommendation for TDM were defined, which range from "strongly recommended" to "not recommended." In a second step, a recommendation tailored to the individual drug was defined.

Levels of recommendations to use TDM as routine monitoring

The therapeutic strategy will only be improved by the use of TDM, if the already mentioned criteria are fulfilled.[60] There is sufficient evidence that TDM can be useful for patients treated with antidepressants, as concluded by the authors of this consensus guideline, after a careful examination of the literature: (i) guidelines; (ii) meta-analyses; (iii) prospective studies on the clinical effectiveness of drugs in which drug plasma concentrations were reported; and (iv) pharmacokinetic studies. However, the latter often do not allow definition of a therapeutic plasma concentration range, in the absence of clinical data. Five levels of recommendation to use

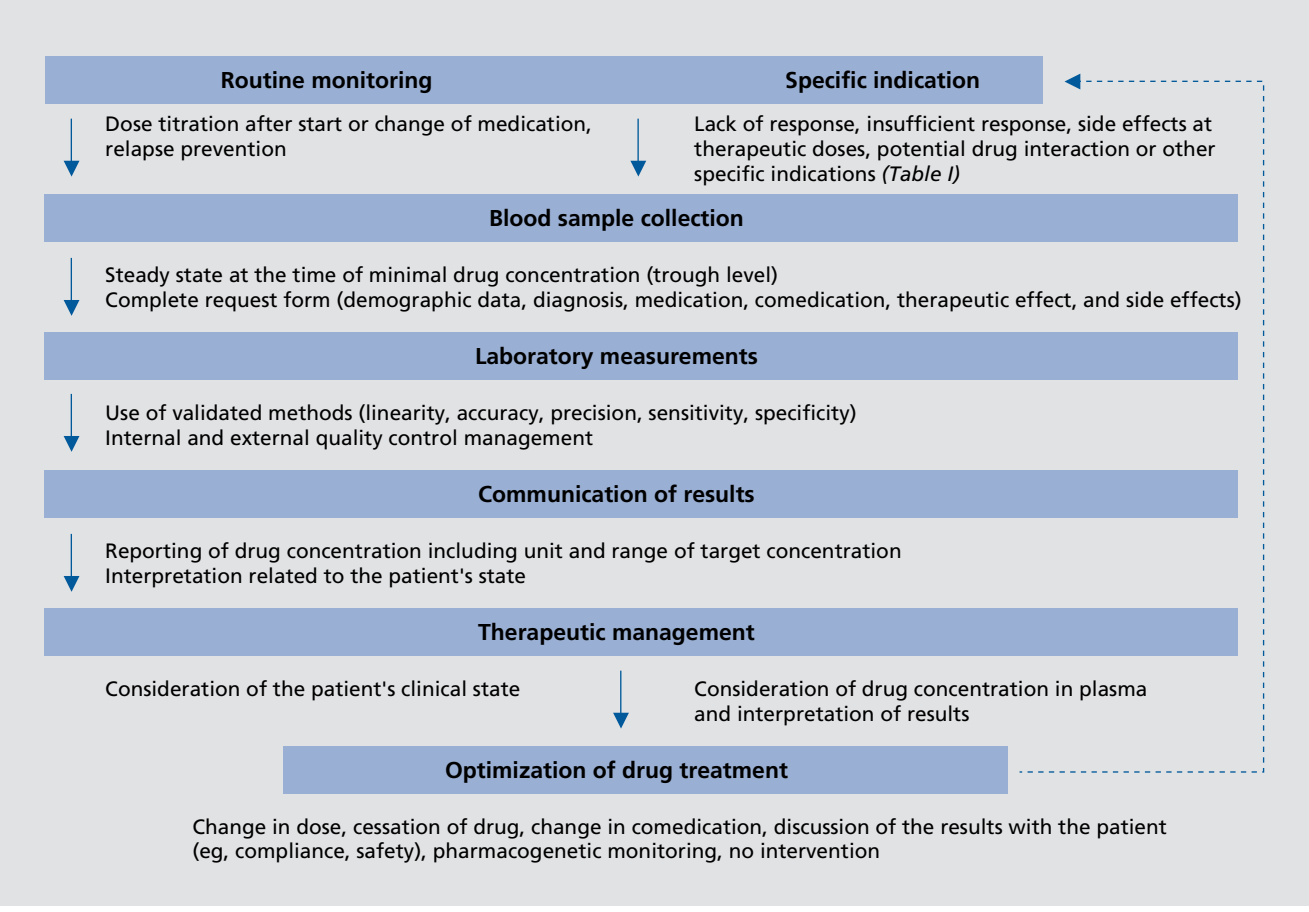

Figure 1. Summary of the therapeutic drug monitoring (TDM) process for optimization of the pharmacotherpy of psychiatric patients. Routine monitoring should be restricted to psychoactive drugs with established therapeutic ranges and who levels of recommendation to use TDM are at least 2 *(Table IV)*. Specific requests may be useful for any psychoactive drug and many indications *(Table I)*, even without well-established therapeutic ranges.[11]

TDM as routine monitoring were defined as follows, as reported earlier.[10]

1. Strongly recommended

- Established therapeutic range
- *Level of evidence*: Controlled clinical trials have shown benefit of TDM; reports on toxic effects at "supratherapeutic" plasma concentrations.
- *Clinical consequences*: At therapeutic plasma concentrations highest probability of response; at "subtherapeutic" plasma concentrations response rate similar to placebo; at plasma concentrations higher than therapeutic concentrations increasing risk of adverse effects.

2. Recommended

- Suggested therapeutic ranges obtained from plasma concentrations at therapeutically effective doses (fixed dose studies).
- *Level of evidence*: At least one well-designed prospective study with well-defined outcome criteria reports intoxications at "supratherapeutic" plasma concentrations.
- *Clinical consequences*: TDM most probably will optimize response in nonresponders: at "subtherapeutic" plasma concentrations risk of poor response; at "supratherapeutic" plasma concentrations risk of adverse effects and/or decreased response.

3. Useful

- Suggested therapeutic ranges are plasma concentrations at effective doses obtained from steady-state pharmacokinetic studies.
- *Level of evidence*: Clinical data from retrospective analysis of TDM data; single case reports; or nonsystematic clinical experience.
- *Clinical consequences*: TDM useful to control whether plasma concentrations are plausible for a given dose; optimizing of clinical response in nonresponders who display low concentrations is possible.

4. Probably useful

- Suggested therapeutic ranges from steady-state pharmacokinetic studies at therapeutically effective doses.
- *Level of evidence*: Valid clinical data so far lacking or inconsistent results.
- *Clinical consequences*: TDM useful to control whether plasma concentrations are plausible for a given dose.

5. Not recommended

- Unique pharmacology of the drug, eg, irreversible blockade of an enzyme or flexible dosing according to clinical symptoms.
- *Level of evidence*: Textbook knowledge, basic pharmacology.
- *Clinical consequences*: TDM should not be used.

Drug-specific TDM recommendations

The knowledge of plasma concentrations ranges observed after treatment of subjects at well-defined doses of the antidepressant *(Table III)* may efficiently help the clinician in some of the situations listed in *Table II*: suspicion of noncompliance, drug interactions, problems occurring after switching from an original preparation to a generic form (and vice versa), or presence of a pharmacogenetic PM or UM status. The information available in *Table III* is also helpful in situations where the levels of recommendations 3 and 4 apply (ie, TDM useful or probably useful).

Suspected noncompliance
Drugs, for which TDM is mandatory for safety reasons (eg, lithium)
Lack of clinical response, or insufficient response, even if dose is considered as adequate
Adverse effects, despite the use of generally recommended doses
Suspected drug interactions
TDM in pharmacovigilance programs
Combination treatment with a drug known for its interaction potential, in situations of comorbidities, "augmentation," etc
Relapse prevention in long-term treatments, prophylactic treatments
Recurrence despite good compliance and adequate doses
Presence of a genetic particularity concerning the drug metabolism (genetic deficiency, gene multiplication)
Children and adolescents
Elderly patients (>65 years)
Patients with pharmacokinetically relevant comorbidities (hepatic or renal insufficiency, cardiovascular disease)
Forensic psychiatry
Problems occurring after switching from an original preparation to a generic form (and vice versa)

Table II. General indications for therapeutic drug monitoring (TDM) of antidepressants.[11]

Antidepressant	Active metabolite (or metabolite recommended for TDM)	Dose-related steady-state plasma concentrations*			
		Dose (mg/day)	Parent compound (ng/mL)	Metabolite (ng/mL)	References
Amitriptyline	Nortriptyline	150	102±59 (34-278)	85±60 (16-326)	Baumann et al,[77] 1986
		150	122±62	84±48	Jungkunz and Kuss,[78] 1980
		150	76±30	84±38	Breyer-Pfaff et al,[79] 1982
		150	100±41	71±38	Breyer-Pfaff et al,[80] 1982
		200	146±21 (sem)	129±23 (sem)	Kupfer et al,[81] 1977
Citalopram	Demethylcitalopram	40	86±38	35±11	Baumann et al,[82] 1996
		40 iv	70±23	30±12	Baumann et al,[83] 1998
Clomipramine	Demethylclomipramine	75 bid	63 md (22-230)*	148 md (51-331)*	Kramer Nielsen et al,[84] 1992
		50	24 md (5-69)*	15 md (6-78)*	DUAG,[85] 1999
		75	38 md (9-78)*	43 md (5-102)*	DUAG,[85] 1999
		125	83 md (31-224)*	105 md (41-335)*	DUAG,[85] 1999
		200	202 md (50-340)*	283 md (138-446)*	DUAG,[85] 1999
		100 iv	122±73	145±118	Müller-Oerlinghausen and Fähndrich,[86] 1985
		150	74-310	69-267	Burch et al,[87] 1982
Desipramine		200	173 (28-882)		Friedel et al,[88] 1979
		186±24	188±152		Amsterdam et al,[89] 1985
		75-250	16-502		Nelson et al,[90] 1985
Dothiepine	Dothiepine-SO	150	95±67	323±191	Maguire et al,[91] 1982
	Northiaden	150		16±12	Maguire et al,[91] 1982
	Dothiepine-SO	3.22±0.99 mg/kg	67 (4-258)	352 (45-953)	Ilett et al,[92] 1993
	Northiaden	3.22±0.99 mg/kg		37 (0-230)	Ilett et al,[92] 1993
Doxepin (DOX)	Demethyldoxepin (DDOX)	250	484±251 nmol/L†		Adler et al,[93] 1997
	Demethyldoxepin	250	130±113	132±94	Deuschle et al,[94] 1997
	trans-Demethyldoxepin	250		72±60	Deuschle et al,[94] 1997
	cis-Demethyldoxepin	250		60±45	Deuschle et al,[94] 1997
		143±30	89±75†		Leucht et al,[95] 2001
Escitalopram‡	*S*-Demethylcitalopram	10‡	27±14	14±5	Bondolfi et al,[96] 1996
		10‡	28±9	11±3	Bondolfi et al,[97] 2000
Fluoxetine	Norfluoxetine	20	80 (9-265) md	126 (30-300) md	Lundmark et al,[98] 2001
		40	195 (40-496) md	221 (20-449) md	
		20	97±51	128±49	Amsterdam et al,[99] 1997
Fluvoxamine		100	90±29 (f)		Härtter et al,[100] 1998
		100	59±22 (m)		Härtter et al,[100] 1998
		200	274±73 (f)		Härtter et al,[100] 1998
		200	237±90 (m)		Härtter et al,[100] 1998
		229±47	142±108 (20-417)		Kasper et al,[101] 1993
		200	162±144 (13-833)		Gerstenberg et al,[102] 2003

Table III. Dose-related steady-state plasma concentrations of antidepressants.[11] Generally, arithmetic means ± standarad deviations are given; numbers in parentheses indicate ranges. md, median value; gm, geometric mean; m, males; f, females. *Extensive metabolizers (CYP 2D6). †Doxepin + desmethyldoxepin. ‡Patients were treated with 20 mg/day citalopram, and *S*-citalopram and its metabolite were measured. §Nonsmokers. ||Smokers. ¶Concentrations given in ng.kg/mL.mg, in extensive metabolizers (CYP 2D6). #Concentrations show very little differences when given 50 mg/day tid.

Antidepressant	Active metabolite (or metabolite recommended for TDM)	Dose (mg/day)	Dose-related steady-state plasma concentrations* Parent compound (ng/mL)	Metabolite (ng/mL)	References
Imipramine	Desipramine	225	(6-268)	(18-496)	Reisby et al,[103] 1977
Maprotiline	(Desmethylmaprotiline)	150	116±47		Gabris et al,[104] 1985
		236±32	202±134 (12-428)		Kasper et al,[101] 1993
Mianserin	Demethylmianserin	30	22 (12-48)	9 (3-24)	Otani et al,[105] 1991
(MIA)	(DMIA)	30	14 (6-37) (*S*-MIA)		Mihara et al,[106] 1997
		30	9 (4-18) (*R*-MIA)		Mihara et al,[106] 1997
		60	37±19 (14-67) (*S*-MIA)	10±5 (6-23) (*S*-DMIA)	Eap et al,[107] 1999
		60	19±11 (10-51) (*R*-MIA)	21±15 (10-52) (*R*-DMIA)	Eap et al,[107] 1999
Mirtazapine	(Demethylmirtazapine)	15	7.3±3.2		Timmer et al,[108] 1995
		30	18±7		Timmer et al,[108] 1995
		45	28±12		Timmer et al,[108] 1995
		60	38±16		Timmer et al,[108] 1995
		70	46±16		Timmer et al,[108] 1995
Moclobemide		100 tid	216±55		Schoerlin et al,[109] 1987
Nortriptyline		150	141±48 (48-238)		
		75-225	90±40 (32-164)		Asberg et al,[12] 1971
Paroxetine		30	36.3 (1.7-60.8)		Lundmark et al,[110] 1989
		30	27 md (12-45)*		Sindrup et al,[111] 1992
		30	36 (9-70)		Kaye et al,[112] 1989
Reboxetine		4	50±20		Pellizzoni et al,[113] 1996
Sertraline	(Norsertraline)	50	12±17 gm (3-134)	30±24 gm (7-143)	Lundmark et al,[114] 2000
		100	19±18 gm (3-109)	45±35 gm (10-273)	Lundmark et al,[114] 2000
		150	31±29 gm (8-145)	65±47 gm (7-138)	Lundmark et al,[114] 2000
		200	29±18 gm (9-82)	87±43 gm (40-189)	Lundmark et al,[114] 2000
		50	12±8 (4-32)		Axelson et al,[115] 2002
Trazodone	*m*-Chlorophenylpiperazine	150	624 (271-1062)	65 (34-108)	Otani et al,[116] 1998
		150	680±257[§]	65±21[§]	Mihara et al,[117] 2001
		150	541±277[‖]	56±21[‖]	Mihara et al,[117] 2001
Trimipramine	Desmethyltrimipramine	200	277±67	169±51	Cournoyer et al,[118] 1987
(TRI)	(DTRI)		21±11 (7-47) (L-TRI)[¶]	7±6 (1-23) (L-DTRI)[¶]	Eap et al,[119] 2000
			18±6 (8-32) (D-TRI)[¶]	10±7 (2-29) (D-DTRI)[¶]	Eap et al,[119] 2000
Venlafaxine	*O*-Demethylvenlafaxine	75 bid[#]	56±31	194±75	Troy et al,[120] 1995
		75	75±93 (5-427)	116±65 (16-260)	Reis et al,[121] 2002
		150	109±232 (4-1903)	186±94 (16-411)	Reis et al,[121] 2002
		225	178±283 (9-1421)	232±132 (63-736)	Reis et al,[121] 2002
		300	155±109 (21-438)	249±121 (104-516)	Reis et al,[121] 2002
Viloxazine		300	1200 (ca 400-1600)		Müller-Oerlinghausen and Ruether,[122] 1979

Table III. Continued.

Drug and active metabolite for antidepressants	Recommended therapeutic range (consensus)	Level of recommendation	References for reports on therapeutic ranges	Reference for reports on intoxications
Amitriptyline plus nortriptyline	80-200 ng/mL	1	Ulrich and Läuter,[60] 2002 Pedersen et al,[123] 1982	Preskorn and Jerkovich,[124] 1990
Citalopram	30-130 ng/mL	3	Bjerkenstedt et al,[125] 1985 Leinonen et al,[126] 1996	Jonasson and Saldeen,[127] 2002
Clomipramine plus norclomipramine	175-450 ng/mL	1	DUAG,[85] 1999 Gex-Fabry et al,[128] 1999 Mavissakalian et al,[129] 1990	McIntyre et al,[130] 1994
Desipramine	100-300 ng/mL	2	Perry et al,[59] 1994 Pedersen et al,[123] 1982	Preskorn and Jerkovich,[124] 1990
Doxepin plus nordoxepin	50-150 ng/mL	3	Leucht et al,[95] 2001 Rodriguez de la Torre et al,[131] 2001	Preskorn and Fast,[132] 1992
Escitalopram	15-80 ng/mL	4	SPC	
Fluoxetine plus norfluoxetine	120-300 ng/mL	3	Lundmark et al,[98] 2001 Amsterdam et al,[99] 1997	
Fluvoxamine	150-300 ng/mL	4	Gerstenberg et al,[102] 2003 Goodnick,[133] 1994	Kasper et al,[101] 1993
Imipramine plus desipramine	175-300 ng/mL	1	Perry et al,[59] 1994	Pedersen et al,[123] 1982
Maprotilin	125-200 ng/mL	3	SPC, Kasper et al,[101] 1993	Pedersen et al,[123] 1982
Mianserin	15-70 ng/mL	3	Montgomery et al,[134] 1978	Isacsson et al,[135] 1997
Mirtazapine	40-80 ng/mL	3	Timmer et al,[136] 2000	Velazquez et al,[137] 2001
Moclobemide	300-1000 ng/mL	4	Fritze et al,[138] 1989 Gex-Fabry et al,[139] 1995	Hernandez et al,[140] 1995
Nortriptyline	70-170 ng/mL	1	Perry et al,[12] 1994 Åsberg et al,[59] 1971	Åsberg et al,[141] 1970
Paroxetine	70-120 ng/mL	3	Lundmark et al,[114] 2000 Tasker et al,[142] 1989	
Reboxetine	10-100 ng/mL	4	Ohman et al,[143] 2001	
Sertraline	10-50 ng/mL	3	Lundmark et al,[114] 2000	Milner et al,[144] 1998
Tranylcypromine	0-50 ng/mL	5	Burke and Preskorn,[145] 1999	Iwersen and Schmoldt,[146] 1996
Trazodone	650-1500 ng/mL	3	Monteleone et al,[147] 1989 Goeringer et al,[148] 2000	
Trimipramine	150-350 ng/mL	3	Cournoyer et al,[118] 1987 Isaccson et al,[135] 1997	
Venlafaxine plus *O*-desmethylvenlafaxine	195-400 ng/mL	2	Veefkind et al,[149] 2000 Levine et al,[150] 1996	
Viloxazine	20-500 ng/mL	3	Norman et al,[151] 1980 Altamura et al,[152] 1986	Falcy et al,[153] 1983

Table IV. Recommended target plasma concentration ranges for antidepressant drugs and levels of recommendation for routine monitoring.[11] Therapeutic ranges indicate trough concentrations of drugs in serum or plasma of patients under steady-state medication. Level of recommendation: 1. *Strongly recommended* (for lithium TDM should be a standard of care): established therapeutic range; 2. *Recommended:* suggested therapeutic ranges obtained from plasma concentrations at therapeutically effective doses (fixed dose studies); 3. *Useful:* suggested therapeutic ranges are plasma concentrations at therapeutically effective doses obtained from steady-state pharmacokinetic studies; 4. *Probably useful:* suggested therapeutic ranges from steady-state pharmacokinetic studies at therapeutically effective doses; 5. *Not recommended*. SPC, Summary of Product Characteristics.

However, the data presented in *Table III* are insufficient to allow levels of recommendations 1 or 2, as it does not include studies on the plasma concentration–clinical effectiveness relationship. Therefore, the literature had to be reexamined to define which antidepressants may get a level 3 or 4 of recommendation for their monitoring. By consensus, a therapeutic range was then also defined for their "main" (= depression) indication *(Table IV)*, as data for other indications (eg, anxiety disorders) are most often lacking, and some studies suggest that optimal ranges may differ, depending on the pathology.[154]
Antidepressants differ widely in their chemical structure and their pharmacological activity, even though most are serotonergic and/or noradrenergic. "Therapeutic windows" have been defined for most tricyclic antidepressants, and TDM is recommended to avoid intoxications, which may be lethal *(Table IV)*.
As regards more recently introduced antidepressants, a clearcut plasma level–clinical effectiveness relationship was not demonstrated for tetracyclic antidepressants (maprotiline, mianserin, or mirtazapine), trazodone, reboxetine, the monoamine oxidase inhibitors moclobemide and tranylcypromine,[133] and SSRIs.[21,155,156] However, TDM of SSRIs was shown to be cost-effective, as it helps to use minimum effective doses.[114] Therefore, data on the plasma concentrations at therapeutic doses may be clinically useful for these drugs *(Table III)*, in situations of noncompliance, nonresponse, adverse effects, or intoxication.

Specific indications for TDM in psychiatry

Therapeutic windows should be interpreted in the context of the clinical situation, before the decision to change treatment strategy is taken. As an example, low levels may be sufficient for the antidepressant doxepin, if it is used to obtain sedation.[95]
Interestingly, despite the increasing use of generics, there are few data available that demonstrate unambiguously the occurrence of pharmacokinetic problems after switching from an original preparation to a generic form (and vice versa).[157-160] TDM is a general indication for the administration of psychotropic drugs in children and adolescents because psychopharmacotherapy of children and adolescents differs from that of adults (Gerlach et al, in press): (i) There are differences in the pharmacokinetic behavior of drugs used in dependence on the stage of development; it is therefore not appropriate to use dosages recommended for adults. (ii) Many drugs are not approved for use in children and adolescents; the consequence is that the criteria for efficacy and safety, guaranteed for the use in adults, are not given for administration in children and adolescents. There is, however, a need to carry out standardized studies to find therapeutic ranges of plasma concentrations for children and adolescents.
In these patients, but also in elderly subjects, TDM may help distinguish between pharmacokinetic and pharmacodynamic factors in the occurrence of adverse effects. Consequently, TDM also represents a useful tool in situations of pharmacovigilance programs.
Antidepressants should be monitored in the blood of pregnant or lactating women in order to minimize drug exposure of the fetus or newborn infant.[161-165]
Investigations on the "therapeutic window" of patients should not only be included in phase IV studies. If possible, they should also be carried out in phase III studies, in relationship with clinical ratings, in order to propose TDM with the introduction of the new drug. As stated in the document published by the European Agency for the Evaluation of Medicinal Products,[166] an established concentration–response relationship is the basis to forecast the chance of toxicity due to pharmacokinetic differences, drug–disease, or drug–drug interactions.

Pharmacogenetic tests in addition to TDM

There is increasing evidence for an advantage to combine pharmacogenetic tests with TDM.[18,39,44,167] However, pharmacogenetic tests alone have limited value, as environmental factors also regulate drug metabolism.[168] Some of the most important indications for phenotyping and/or genotyping (in combination with TDM) are the following.[51,168]

- The metabolism of the medication (or its active metabolite) is governed to a significant extent by the enzyme, which is considered to be phenotyped or genotyped.
- The patient is treated with a substrate whose metabolism shows a wide interindividual variability, as demonstrated by TDM.
- A drug is characterized by a low therapeutic index, ie, risk of toxicity in the case of a genetically impaired metabolism or, on the other hand, risk of nonresponse due to an ultrarapid metabolism and the inability to reach therapeutic drug levels.
- The patient presents unusual plasma concentrations of the drug or its metabolite(s), and genetic factors are suspected to be responsible.

- The patient suffers from a chronic illness, which requires life-long treatment.

As outlined above, both phenotyping and genotyping are recommended in some circumstances, as a "trait-marker" and a "state-marker." Currently, data obtained by TDM represent a "state-marker."

Practical aspects of TDM

Previous studies suggest that the "compliance" of the treating physician needs to be improved, as many requests or indications for TDM were inappropriate.[169] Moreover, clinicians frequently do not follow the recommendations given by the laboratory to adjust the treatment.[73] Therefore, some practical recommendations are summarized (see reference 11 for a comprehensive presentation) for the optimal use of TDM, as illustrated in *Figure 1*.

Recommendations for the treating physician

Preparation of TDM

Some patients may particularly benefit from TDM: an antidepressant drug should then be recommended for which TDM is available, either to minimize adverse effects or optimize its clinical efficacy. A well-defined "therapeutic window" for this drug *(Table IV)* or at least known plasma concentration ranges for clinical doses *(Table II)* should be available.

Blood should be collected for TDM in steady-state conditions, ie, at least 5 drug half-lives after changes in dose and during the terminal β-elimination phase. Generally, the appropriate sampling time for most antidepressants (except for fluoxetine) is 1 week after stable daily dosing and immediately before ingestion of the morning dose, ie, about 12 to 16 h (or 24 h if the drug is given once daily) after the last medication. It should be considered that both after a modification of the dose and after prescription of a comedication, which may inhibit or enhance the metabolism of the drug to be measured, steady-state conditions are reached again only after a few days. TDM should then be delayed, in case unexpected side effects are observed.

Most antidepressants are stable in serum or plasma for at least 24 h[170] and can therefore be sent to the laboratory at room temperature. It is mandatory to consider technical recommendations given by the laboratory: choice of anticoagulant (plasma, serum), sample volume and its labeling, conditions for mailing, influence of light, and temperature. Information on comedication may help the laboratory to avoid analytical problems (interferences with other drugs). It is strongly recommended to fill out the request forms adequately and completely (diagnosis, comorbidities, comedications, treatment duration, doses, sex and age of the patient, and reasons for the request), in order to allow interpretation of the result by clinical pharmacologists. Some of these data may also represent important information for the laboratory to judge plausibility of the result.

Critical appreciation of the results

A pharmacological treatment should be guided by sound clinical judgment. TDM has to be considered as an additional and useful tool for optimizing therapy.

Analytical methods used in the laboratories may differ in their quality. The physician should be aware that some drug levels are not accurately measured, even though most laboratories have introduced a program to measure quality. Indeed, worldwide external quality-control programs show considerable variability between laboratories in the results of analysis of control samples. The physician may obtain discrepant results when a drug was monitored several times in a patient, but analyzed in different laboratories. When comparisons of TDM values obtained from different laboratories are carried out, the clinician should take into account the units (ng/mL, µg/L, µmol/L, nmol/L) in which the results of the analysis are expressed.

Low plasma drug concentrations suggest either irregular intake of the drug or ultrarapid metabolism, and in this situation, a pharmacogenetic test may be indicated. In the first case, TDM should be repeated in order to verify compliance. These examples show that it may be advantageous for the clinician to collaborate with a TDM laboratory that offers pharmacological consultation.

TDM interpretation and treatment of patients

A TDM result represents a guide to adjust the treatment of the individual patient, but expert interpretation and adequate use of this pharmacokinetic data are mandatory for an optimal clinical benefit. Reporting of results and inclusion of dose recommendations and other com-

ments by the laboratory must be guided by the best available evidence. However, the laboratory has only limited knowledge of the clinical context. The physician should also take into consideration whether the "reference plasma concentrations range" reflects only "drug plasma concentrations at clinically relevant doses" *(Table III)* or whether they are "therapeutic ranges" *(Table IV)*. Information on the level of recommendation for TDM of the particular drug may also help evaluate the clinical significance of the result *(Table IV)*. If the plasma concentration of the drug is within the therapeutic range, an adaptation of the dose is, of course, only recommended when clinical reasons, such as adverse effects or nonresponse, clearly justify such a decision. When the advice given on the TDM report is not followed, the reason for such a decision should be carefully documented.

Recommendations for the laboratory

Analytical procedures

The concentrations of antidepressants are generally low, in the ng/mL range, and many patients are comedicated with various, potentially interfering drugs. The methods should be adapted to this situation by precision (coefficient of variation <15%), accurateness (deviation from nominal value <15%), and robustness.[5] Each assay needs to be validated, documented, and regularly assessed for linearity, selectivity, accuracy, precision, recovery, and sensitivity (limits of detection [LOD] and quantification [LOQ]). Internal and external quality control procedures are mandatory to ensure maximal quality of TDM. If quality controls are outside the expected range, the reason underlying the outlier needs to be clarified and documented.[64-66]

Where indicated the laboratory should analyze both the drug and its active metabolite(s) *(Tables II and III)*. Moreover, the analysis of (active and inactive) metabolites represents an additional tool to verify compliance of patients.

Reporting of results

In addition to the result, the appropriate target range should be communicated to the physician *(Tables II and III)*, using, of course, the same units (either mass or molar units). The LOD, or preferentially the LOQ, should be indicated in situations when plasma drug concentrations are below these values. The results should be available for clinical interpretation within a clinically meaningful time, especially in case of suspected intoxications. An interpretation and clinical and pharmacological advice should be provided with every report. Therefore, it is advantageous for the clinician to choose a laboratory that offers this service.

Plasma concentrations must be interpreted in the light of sound clinical judgment. Most frequently, recommendations on dose changes are given, and in a situation of drug concentrations above the recommended range, rapidity of communication may enhance successful intervention in patients at risk of toxicity. The physician will also appreciate comments related to genetic polymorphisms, risk for pharmacokinetic interactions in situations, and pharmacokinetic properties of the drug when given to elderly patients or patients with hepatic or renal insufficiency.

In situations where drug concentrations are particularly low, it is often not clear whether the patient is an UM or whether he or she is noncompliant in that the drug intake is irregular. The analysis of a second plasma sample may help verify compliance but, depending on the result, a pharmacogenetic test should be carried out.

Clearly a PM (CYP 2D6) status should not automatically result in interruption of a treatment,[18,171] but the dose should be adapted using clinical judgment and TDM.

Conclusion

TDM is a valuable approach to optimize both short-term and lifelong treatment of psychiatric patients with antidepressants,[172] and a combination of TDM with pharmacogenetic tests will be increasingly useful, particularly because in near future, pharmacogenetic tests regarding pharmacodynamic parameters will also be clinically relevant.[173] Many data on plasma concentrations of psychotropic drugs and the plasma concentration–clinical effectiveness relationship have accumulated over the past few years, and encouraged this interdisciplinary collaboration of specialists who brought about this consensus on TDM.[11] Hopefully, it will help to use TDM optimally from a scientific, clinical, and economic point of view. ❑

Las pautas de consenso del grupo de expertos AGNP-TDM: foco en el monitoreo terapéutico de los antidepresivos

El monitoreo terapéutico de fármacos (TDM), que incluye los antidepresivos entre los psicofármacos, se ha introducido extensamente para optimizar la farmacoterapia en los pacientes psiquiátricos. El grupo interdisciplinario de TDM del Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie *(AGNP) ha trabajado en pautas de consenso con el objetivo de entregar a los psiquiatras y a los laboratorios de TDM una herramienta que permita optimizar el empleo del TDM. Se definieron cinco niveles de recomendación basados en la investigación relacionada con el monitoreo de rutina de concentraciones plasmáticas de fármacos: (1) altamente recomendado, (2) recomendado, (3) útil, (4) probablemente útil y (5) no recomendado. Además se presentó una lista de indicaciones que justifican el uso del TDM, como por ejemplo, el control de la adherencia, la falta de respuesta clínica o los efectos adversos a dosis recomendadas, las interacciones de fármacos, los programas de farmacovigilancia, la presencia de alguna particularidad genética en relación con el metabolismo de los fármacos y los pacientes infanto-juveniles y ancianos. Para algunos fármacos faltan estudios en rangos terapéuticos. De acuerdo con estudios farmacocinéticos reportados en la literatura, se presentan los rangos objetivos para concentraciones plasmáticas clínicamente relevantes de la mayoría de los fármacos. Para muchos antidepresivos un completo análisis de la literatura de los estudios que abordan la relación concentración plasmática–eficacia clínica ha permitido la inclusión de rangos terapéuticos de concentraciones plasmáticas. Además, se han realizado recomendaciones relacionadas con la combinación de pruebas farmacogenéticas (fenotipo o genotipo) con el TDM. Finalmente, se han entregado instrucciones prácticas para los profesionales de los laboratorios y los psiquiatras tratantes de cómo utilizar el TDM: preparación del TDM, análisis de fármacos, informe e interpretación de resultados y un adecuado uso de la información para el tratamiento del paciente. El TDM es un proceso complejo que requiere de una óptima coordinación interdisciplinaria de un procedimiento que involucra pacientes, psiquiatras tratantes, farmacólogos clínicos y especialistas en laboratorio clínico. Esta pauta de consenso debiera ser útil para optimizar el TDM de los antidepresivos.*

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Recommandations du groupe d'experts AGNP-TDM: Le monitoring à but thérapeutique des antidépresseurs

*Le dosage plasmatique de médicaments psychotropes dans un but thérapeutique (*therapeutic drug monitoring *(TDM)) y compris des antidépresseurs a été largement introduit pour optimiser la pharmacothérapie de patients psychiatriques. Le groupe interdisciplinaire AGNP-TDM* (Arbeitsgemeinschaft für Neuropsychopharmakologie und Phamakopsychiatrie; Association de Neuro-psycho-pharmacologie et de Pharmacopsychiatrie) *a élaboré des recommandations dans le but de procurer aux psychiatres et aux laboratoires TDM un outil pour optimiser l'utilisation du TDM. Basés sur des résultats obtenus par la recherche, cinq niveaux de recommandations ont été définis par rapport au monitoring de routine des taux plasmatiques de médicaments : 1. fortement recommandé, 2. recommandé, 3. utile, 4. probablement utile, 5. pas recommandé. De plus une liste d'indications qui justifient l'utilisation des TDM est présentée, par exemple : contrôle de l'observance, absence de réponse clinique ou effets secondaires à des doses généralement recommandées, interactions médicamenteuses, programme de pharmacovigilance, présence d'une particularité génétique concernant le métabolisme de médicaments, enfants, adolescents et patients âgés. Pour quelques médicaments, des études sur les marges thérapeutiques manquent, mais des marges cibles pour des concentrations plasmatiques cliniquement significatives sont présentées pour la plupart des médicaments, basées sur des études pharmacocinétiques rapportées dans la littérature. Pour beaucoup d'antidépresseurs, une analyse complète de la littérature sur les études qui traitent de la relation concentration plasmatique – efficacité clinique a permis de présenter des marges thérapeutiques de concentrations plasmatiques. En outre, des recommandations sont données par rapport à la combinaison de tests pharmacogénétiques (phénotypage ou génotypage) avec le TDM. Finalement, des instructions pratiques sont données aux techniciens responsables de laboratoires et aux médecins traitants qui utilisent le TDM : préparation du TDM, analyses de médicaments, communication et interprétation du résultat et utilisation adéquate de l'information pour le traitement du patient. Le TDM est un processus qui nécessite une coordination interdisciplinaire optimale d'une procédure qui implique des patients, des médecins traitants, des pharmacologues cliniques et des spécialistes du laboratoire clinique. Ce* « Consensus guideline » *(recommandations) devrait être utile pour optimiser le TDM d'antidépresseurs.*

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